

Claims:

1. A parasitological spot-on formulation, which comprises:
 - a) an effective amount of an ectoparasitological combination comprising an 1-N-arylpyrazole derivative and amitraz;
 - b) a pharmaceutical or veterinary acceptable liquid carrier vehicle; and
 - c) optionally, a crystallization inhibitor.
2. The parasitological spot-on formulation according to claim 1, wherein
 - the liquid carrier vehicle comprises a solvent and a cosolvent wherein the solvent is selected from the group consisting of acetone, acetonitrile, benzyl alcohol, butyl diglycol, dimethylacetamide, dimethylformamide, dipropylene glycol n-butyl ether, ethylene glycol monoethyl ether, ethylene glycol monomethyl ether, monomethylacetamide, dipropylene glycol monomethyl ether, liquid polyoxyethylene glycols, propylene glycol, 2-pyrrolidone, diethylene glycol monoethyl ether, ethylene glycol, diethyl phthalate fatty acid esters, and a mixture of at least two of these solvents and the cosolvent is selected from the group consisting of ethanol, isopropanol and methanol.
 - the crystallization inhibitor selected from the group consisting of an anionic surfactant, a cationic surfactant, a non-ionic surfactant, an amine salt, an amphoteric surfactant or polyvinylpyrrolidone, polyvinyl alcohols, copolymers of vinyl acetate and vinylpyrrolidone, polyethylene glycols, benzyl alcohol, mannitol, glycerol, sorbitol, polyoxyethylenated sorbitan esters, lecithin, sodium carboxymethylcellulose, and acrylic derivatives, and a mixture of these crystallization inhibitors.

3. The parasitical spot-on composition according to claim 2, wherein the formulation further comprises an antioxidant.

4. The parasitical spot-on composition according to claim 3, wherein the antioxidant is selected from the group consisting of butylated hydroxyanisole, butylated hydroxytoluene, ascorbic acid, sodium metabisulphite, propyl gallate and sodium thiosuphate.

5. The parasitical spot-on formulation according to claim 2, wherein water is present in a proportion of from 0 to about 30% v/v.

6. The parasitical spot-on formulation according to claim 2, wherein the crystallization inhibitor is present in an amount from about 1 to about 20% w/v.

7. The parasitical spot-on formulation according to claim 1 which comprises a crystallization inhibitor.

8. The parasitical spot-on formulation according to claim 2, wherein

- the anionic surfactant is alkaline stearates, sodium abietate; alkyl sulphates; sodium dodecylbenzenesulphonate, sodium dioctylsulphosuccinate, and fatty acids;

- the cationic surfactant is water-soluble quaternary ammonium salts of formula $N^+R'R''R'''Y^-$ in which the radicals R independently are hydrocarbon radicals, optionally hydroxylated, and Y^- is an anion of a strong acid;

- the amine salt is an amine salt of $N^+R'R''R'''$ in which the radicals R independently are optionally hydroxylated hydrocarbon radicals;

- the non-ionic surfactant is optionally polyoxyethylenated sorbitan esters, polyoxyethylenated alkyl ethers, polyethylene glycol stearate, polyoxyethylenated

derivatives of castor oil, polyglycerol esters, polyoxyethylenated fatty alcohols, polyoxyethylenated fatty acids, copolymers of ethylene oxide and propylene oxide; and

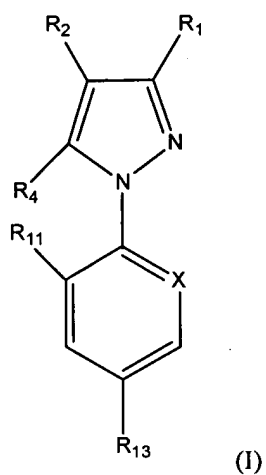
- the amphoteric surfactant is lauryl-substituted betaine compounds.

9. The parasitical spot-on formulation according to claim 3, wherein the crystallization inhibitor is a crystallization inhibitor system comprising a polymeric film-forming agent and a surfactant.

10. The parasitical spot-on formulation according to claim 3, wherein the polymeric film-forming agent is polyvinylpyrrolidone, polyvinyl alcohols, or a copolymer of vinyl acetate and polyvinylpyrrolidone and the surfactant is a non-ionic surfactant.

11. The parasitical spot-on formulation according to claim 10, wherein the crystallization inhibitor system is a mixture of polyvinylpyrrolidone and polyoxethylene (20) sorbitan mono-oleate.

12. The parasitical spot-on formulation according to claim 1, wherein the 1-N-aryl pyrazole is a compound of the formula



in which

R_1 is a halogen atom, CN or alkyl;

R_2 is $S(O)_nR_3$ or 4,5-dicyanoimidazol-2-yl or haloalkyl;

R_3 is alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, or haloalkynyl;

R_4 represents a hydrogen or halogen atom or an NR_5R_6 , $S(O)_mR_7$, $C(O)R_7$, $C(O)OR_7$, alkyl, haloalkyl, OR_8 , or an $-N=C(R_9)(R_{10})$ group;

R_5 and R_6 independently represent a hydrogen atom or an alkyl, haloalkyl, $C(O)alkyl$, $S(O)_rCF_3$ or alkoxy carbonyl radical or R_5 and R_6 can together form a divalent alkylene radical which is optionally interrupted by one or two divalent heteroatoms;

R_7 represents an alkyl or haloalkyl group;

R_8 represents an alkyl or haloalkyl group or a hydrogen atom;

R_9 represents an alkyl group or a hydrogen atom;

R_{10} represents an optionally substituted aryl or an optionally substituted heteroaryl group;

R_{11} and R_{12} represent, independently of one another, hydrogen, halogen, CN or NO_2 ;

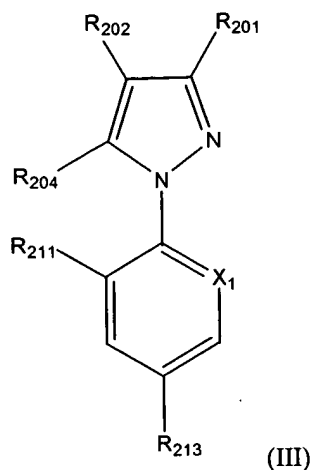
R_{13} represents a halogen atom or a haloalkyl, haloalkoxy, $S(O)_qCF_3$ or SF_5 group;

m , n , q and r represent, independently of one another, an integer equal to 0, 1 or 2;

X represents a trivalent nitrogen atom or a $C-R_{12}$ radical, the three other valencies of the carbon atom forming part of the aromatic ring;

with the proviso that, when R_1 is methyl, then either R_3 is haloalkyl, R_4 is NH_2 , R_{11} is Cl, R_{13} is CF_3 and X is N or else R_2 is 4,5-dicyanoimidazol-2-yl, R_4 is Cl, R_{11} is Cl, R_{13} is CF_3 and X is C-Cl, or an acceptable salt thereof.

13. The parasiticol spot-on formulation according to claim 1, wherein the 1-N-aryl pyrazole is a compound of the formula



wherein:

R_{201} is cyano, $C(O)alkyl$, $C(S)NH_2$, alkyl, $C(=NOH)NH_2$ or $C(=NNH_2)NH_2$;

R_{202} is $S(O)_hR_{203}$, C_2-C_3 alkenyl, C_2-C_3 haloalkenyl, cycloalkyl, halocycloalkyl or C_2-C_3 alkynyl;

R_{203} is alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl or haloalkynyl;

R_{204} is $-N(R_{205})C(O)CR_{206}R_{207}R_{208}$, $-N(R_{205})C(O)aryl$, or $-N(R_{205})C(O)OR_{207}$;

R_{205} is alkyl, haloalkyl, cycloalkyl, halocycloalkyl, cycloalkylalkyl, halocycloalkylalkyl, alkoxyalkyl, haloalkoxyalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl;

R_{206} is hydrogen, halogen, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, formyloxy, alkylcarbonyloxy, haloalkylcarbonyloxy, alkylthio, haloalkylthio, alkylsulfinyl, haloalkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, alkylamino, dialkylamino, haloalkylamino, di(haloalkyl)amino, cycloalkyloxy, halocycloalkyloxy, alkoxyalkoxy, haloalkoxyalkoxy, alkoxyalkoxyalkoxy, aryloxy, or arylalkoxy;

R_{207} and R_{208} are independently hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl; or R_{207} and R_{208} may form together with the carbon to which they are attached a 3- to 7- membered ring which additionally may contain one or more heteroatoms selected from nitrogen, oxygen and sulfur;

X_1 is selected from nitrogen and C- R_{212} ;

R_{211} and R_{212} are independently selected from halogen, hydrogen, CN and NO_2 ;

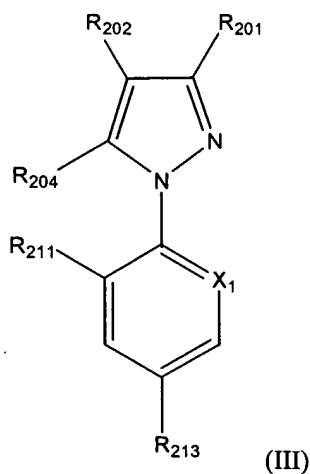
R_{213} is selected from halogen, haloalkyl, haloalkoxy, $-S(O)_kCF_3$, and $-SF_5$;

and

h and k are independently selected from 0, 1, and 2;

or an acceptable salt thereof.

14. The parasitical spot-on formulation according to claim 1, wherein the 1-N-arylpyrazole derivative is a compound of the formula



wherein:

R₂₀₁ is cyano, C(O)alkyl, C(S)NH₂, alkyl, C(=NOH)NH₂ or C(=NNH₂)NH₂;

R₂₀₂ is S(O)_hR₂₀₃, C₂-C₃ alkenyl, C₂-C₃ haloalkenyl, cycloalkyl, halocycloalkyl or C₂-C₃ alkynyl;

R₂₀₃ is alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl or haloalkynyl;

R₂₀₄ is -N(R₂₀₅)C(O)CR₂₀₆R₂₀₇R₂₀₈, -N(R₂₀₅)C(O)aryl, or -N(R₂₀₅)C(O)OR₂₀₇;

R₂₀₅ is alkyl, haloalkyl, cycloalkyl, halocycloalkyl, cycloalkylalkyl, halocycloalkylalkyl, alkoxyalkyl, haloalkoxyalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl;

R₂₀₆ is hydrogen, halogen, alkoxy, haloalkoxy, alkoxyalkyl, haloalkoxyalkyl, formyloxy, alkylcarbonyloxy, haloalkylcarbonyloxy, alkylthio, haloalkylthio, alkylsulfinyl, haloalkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, alkylamino, dialkylamino, haloalkylamino, di(haloalkyl)amino, cycloalkyloxy, halocycloalkyloxy, alkoxyalkoxy, haloalkoxyalkoxy, alkoxyalkoxyalkoxy, aryloxy, or arylalkoxy;

R₂₀₇ and R₂₀₈ are independently hydrogen, alkyl, haloalkyl, cycloalkyl, or halocycloalkyl; or R₂₀₇ and R₂₀₈ may form together with the carbon to which they are attached a 3- to 7- membered ring which additionally may contain one or more heteroatoms selected from nitrogen, oxygen and sulfur;

X₁ is selected from nitrogen and C-R₂₁₂;

R₂₁₁ and R₂₁₂ are independently selected from halogen, hydrogen, CN and NO₂;

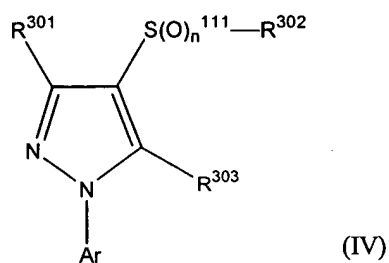
R₂₁₃ is selected from halogen, haloalkyl, haloalkoxy, -S(O)_kCF₃, and -SF₅;

and

h and k are independently selected from 0, 1, and 2;

or an acceptable salt thereof.

15. The parasitocal spot-on formulation according to claim 1, wherein the 1-N-arylpyrazole derivatives is a compound of the formula:

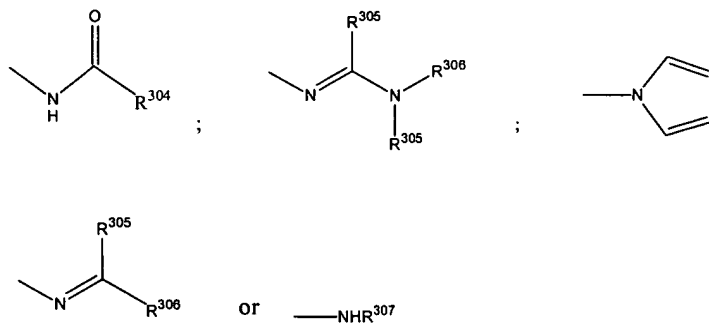


in which

R^{301} is $H_2N-C(S)-$,

R^{302} is halogenoalkyl, halogenoalkenyl or halogenoalkynyl,

R^{303} is hydrogen, amino or one of the following groups:



where

R³⁰⁴ represents alkyl, halogenoalkyl, alkoxyalkyl or in each case optionally substituted phenyl or pyridyl,

R³⁰⁵ represents hydrogen or alkyl,

R³⁰⁶ represents hydrogen, alkyl or in each case optionally substituted phenyl or pyridyl and

R³⁰⁷ represents alkyl, alkenyl, alkynyl, formyl, alkylcarbonyl, halogenoalkylcarbonyl or alkoxy carbonyl;

Ar represents in each case optionally substituted phenyl or pyridyl, and

a represents a number 0, 1 or 2,

or an acceptable salt thereof.

16. The parasiticaI spot-on formulation according to claim 1, wherein the formulation further comprises an insect growth regulator.

17. The parasiticaI formulation according to claim 16, wherein the insect growth regulator mimics juvenile hormones.

18. The parasiticaI formulation according to claim 17, wherein the insect growth regulator is selected from the group consisting of azadirachtin, diofenolan, fenoxycarb, hydroprene, kinoprene, methoprene, pyriproxyfen, tetrahydroazadirachtin, and 4-chloro-2-(2-chloro-2-methyl-propyl)-5-(6-iodo-3-pyridylmethoxy)pyridizine-3(2H)-one.

19. The parasiticaI formulation according to claim 16, wherein the insect growth regulator inhibits chitin synthesis.

20. The parasitological formulation according to claim 19 wherein the insect growth regulator is selected from the group consisting of chlorfluazuron, cyromazine, diflubenzuron, and fluazuron.

21. The parasitological formulation according to claim 1, wherein the 1-N-arylphenyl pyrazole is fipronil, the pharmaceutically or veterinary acceptable carrier is diethyleneglycol monoethyl ether, the crystallization inhibitor is polyvidone, the surfactant is polysorbate 80 and the antioxidant is butylated hydroxyanisole and butylated hydroxytoluene.

22. The parasitological formulation according to claim 1, which further comprises at least one milbemycin or avermectin derivative, imidazothiazide anthelmintic, benzimidazole anthelmintic, or a pyrethroid.

23. A parasitological pour-on formulation, which comprises:

- a) an effective amount of an ectoparasitological combination comprising an 1-N-aryl pyrazole derivative and amitraz;
- b) a pharmaceutical or veterinary acceptable liquid carrier vehicle;
- c) optionally, a crystallization inhibitor;
- d) optionally, an antioxidant.

24. The parasitological pour-on formulation according to claim 23, wherein

- the pharmaceutically or veterinary acceptable liquid carrier vehicle which comprise a solvent and a cosolvent wherein the solvent is selected from the group consisting of a acetone, a acetonitrile, benzyl alcohol, butyl diglycol, dimethylacetamide, dimethylformamide, dipropylene glycol n-butyl ether, ethylene glycol monoethyl ether, ethylene glycol monomethyl ether, monomethylacetamide, dipropylene glycol monomethyl ether, liquid polyoxyethylene glycols, propylene glycol, 2-pyrrolidone,

diethylene glycol monoethyl ether, ethylene glycol, diethyl phthalate, fatty acid esters and a mixture of at least two of these solvents and the cosolvent is selected from the group consisting of absolute ethanol, isopropanol and methanol; and

- a crystallization inhibitor selected from the group consisting of an anionic surfactant, a cationic surfactant, a nonionic surfactant, anamine salts, amphoteric surfactant, polyvinylpyrrolidone, polyvinyl alcohols, copolymers of vinyl acetate and vinylpyrrolidone, polyethylene glycols, benzyl alcohol, mannitol, glycerol, sorbitol, polyoxyethylenated sorbitan esters; lecithin, sodium carboxymethylcellulose, acrylic derivatives and a mixture of these crystallization inhibitors.

25. The parasitical pour-on formulation according to claim 24, wherein the 1-N-arylpyrazole is fipronil.

26. The parasitical pour-on formulation according to claim 23, which further comprises at least one milbemycin or avermectin derivative, imidazothiazide anthelmintic, benzimidazole anthelmintic, or a pyrethroid.

27. The parasitical pour-on formulation according to claim 23, wherein the formulation further comprises an insect growth regulator.

28. A parasitical spray formulation which comprises

- a) an effective amount of an ectoparasitical combination comprising a 1-N-aryl pyrazole derivative and amitraz; and
- b) a pharmaceutical or veterinary acceptable liquid carrier vehicle.

29. A method for preventing, controlling, or eliminating parasites in a mammal or bird in need thereof which comprises applying a effective amount of the spot-on formulation according to claim 1 to the mammal or bird.

30. The method according to claim 29, wherein antiparasitical activity lasts for an extended duration.

31. The method according to claim 30, wherein the extended duration is from one month to three months.

32. The method according to claim 30, wherein the 1-aryl-pyrazole is fipronil and the mammal is a cat or a dog and the parasites are fleas and/or ticks.

33. A method for preventing, controlling or eliminating parasites in a mammal or bird in need thereof which comprises applying an effective amount of the pour-on formulation according to claim 24 to the mammal or bird.

34. The method according to claim 33, wherein the antiparasitical activity lasts for an extended duration.

35. The method according to claim 34, wherein the extended duration is from one month to three months.

36. The method according to claim 34, wherein the extended duration is from two months to three months.

37. The method according to claim 33, wherein the 1-aryl-pyrazole is fipronil and the mammal is a cat or a dog and the parasites are fleas and/or ticks.

38. A method for preventing, controlling or eliminating parasites in a mammal or bird in need thereof, which comprises applying the parasite spray formulation according to claim 29 to said mammal or bird.

39. The method according to claim 38, wherein the antiparasitical activity lasts for an extended duration.

40. The method according to claim 39, wherein the extended duration is from 1 month to three months.

41. The method according to claim 39, wherein the extended duration is from two months to three months.

42. The method according to claim 38, wherein the 1-aryl-pyrazole is fipronil and the mammal is a cat or a dog and the parasites are fleas and/or ticks.

43. A method for increasing the onset of activity of a parasitological formulation comprising a 1-N-arylpyrazole derivative, which comprises adding an effective amount of amitraz to said formulation.

44. A method for treating animal housing for parasitological infestations which comprises applying a parasitological formulation which comprises an ectoparasitological combination comprising a 1-N-arylpyrazole derivative, a pharmaceutical or veterinary acceptable liquid carrier vehicle and, optionally a crystallization inhibitor.

45. The method according to claim 44, wherein the animal housing is dog or cat bedding, horse stables, and chicken litter.

